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METHEMOGLOBINEMIA

Case Report No. 91

Frank J. Murphy, M.D.
Francis L. Zinzi, M.D.
Lois Murphy, M.D.

G. P. 47-586

A two year old white female was admitted to the hospital on January 16, 1947 because of cyanosis of several hours duration.

The patient, as stated by the mother, had been in good health until one week prior to entry when she developed a mild upper respiratory infection from which she was recovering at the time of her present illness. The patient had taken no medication during her illness. Past history and family history were non-contributory.

About 10:30 the morning of admission the patient was observed by a sister to eat a yellow wax crayon. The mother, when informed, was not particularly concerned because her children had eaten crayons before without injurious effect. A short time later the child had her lunch and then had an early afternoon nap, in the same room with a younger sibling. About a half hour later at 1:30 P.M. the mother responded to the child's scream and found her crying and she appeared very pale. The patient then seemed to "turn blue" before the mother's eyes. A physician saw the girl soon after the onset of these symptoms and referred her to this hospital immediately. The child became nauseated and vomited once on the way. The vomitus was described by the mother as undigested food containing particles of yellow crayon.

Physical examination revealed a mottled cyanotic child, at first impression very closely resembling the mottled appearance of a cadaver, but in no evident distress. The skin was surprisingly warm except for the distal portions of the extremities which were cool. The temperature was 98.6°F., B.P. 88/60. The cardiac rate was 180 and regular. The ear drums and pharynx were slightly injected. The chest was clear. There were no murmurs noted. The liver edge was rounded and palpable 3 cm. below the costal margin at the mid-clavicular line. There was no lymphadenopathy. The reflexes were normal and the child responded to stimuli very quickly.

Gastric lavage in the Admission Room revealed yellowish fluid with particles of yellow material which were thought to be crayon.

Laboratory examination showed 8 gms. % of hemoglobin, 3,700,000 erythrocytes, 18,000 leucocytes with a differential of 61% neutrophiles, 30% lymphocytes, 1% monocytes and 8% eosinophiles. There were 300,000

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thrombocytes. Urinalysis was negative. The venous pressure was 225 mm. of saline. Blood culture was negative. Spectroscopic examination of the blood by the National Institute of Health[1] revealed 3.9 gm. % of methemoglobin. Blood smears showed the presence of blue granules in many erythrocytes (Heinz bodies).

X-ray examination of the chest revealed the presence of a full sized heart of normal contour with considerable congestion throughout the lung parenchyma.

Immediate therapy consisted of placing the child in an oxygen tent. About 2 hours after admission the patient was given 1.5 cc. of a 1% solution of methylene blue by vein with an almost immediate lessening of cyanosis. Because of the possibility of cardiac failure, rapid intravenous digitalization was accomplished and followed by a transfusion of 150 cc. of whole citrated blood. Several hours later the patient appeared moderately pale with but slight clinical evidence of cyanosis. On the third hospital day X-ray of the chest showed absence of the previously described congestion but some increase in bronchovascular markings. Cardiac consultation on the eighth hospital day revealed no proof of heart disease and it was pointed out that the only evidence of heart failure and temporary myocarditis had been the high venous pressure.

The child developed a purulent otitis media which responded readily to penicillin therapy and was discharged on the nineteenth hospital day.

DISCUSSION

Neuland[2] in 1921 reported two cases of methemoglobinemia in newborns from the same baby ward. "Inspection of the diapers showed a number of black identification marks. Examination of the blood showed methemoglobin confirmed by spectroscopic examination. The blood findings on the same day showed in a great number of red blood cells the blue granules which have been observed so far only in the case of poisons forming methemoglobin."

Referring to acute aniline poisoning Neuland stated that the seriousness of the affection depends not only on the amount which was absorbed but also on the individual sensitivity. This author reviewed the literature on aniline poisoning, stating that the Dutch had reported a number of poisonings due to shoe polish containing aniline and pointed out that comparatively small amounts suffice for acute poisoning. Karger reported a case which showed that aniline invades the system not only through the skin but also through the stomach. This author stated that the typical discoloration of the skin was the first manifestation. The discoloration may appear as early as 10 minutes or as late as 8 hours after the absorption. The poisoning ends in death in a few hours or in recovery.

During the past year several reports have appeared in the literautre concerning methemoglobinemia. Scott et al. [3] reported two outbreaks of dye poisoning in infants, due to diapers and wash cloths which were stamped with ink containing aniline oil. The articles were used before being laundered. Faucett and Mills[4] reported two cases of methemoglobinemia occurring in infants whose formulas contained well water of high nitrate content. Ferrant[5] reported two additional cases with the same etiology. Govan[6] in unpublished material has observed methemoglobinemia occurring in several children who had been known to have ingested crayons.

Our case is unusual because the methemoglobinemia was apparently due to an ingredient of the ingested wax crayon. While ingestion of wax crayons is a common occurrence with pre-school children, toxic effects are uncommon. The following attempts were made to support this theory. Correspondence with the manufacturers of the crayon revealed the following information. "Non-toxic benzidine yellow lake is used in our crayons. Benzidine is non-toxic and generally considered so. No dyes are used. Other components are paraffin, stearic acid and clay. Crayon is insoluble in water due to the fact that each color particle is covered with wax. These crayons are not dissolved by gastric juices of the stomach for the above reason, in other words, are not digestible."

We were able to obtain the remaining portion of the crayon which the child had ingested and it was sent to the Food and Drug Administration for further analysis. This in part was their report:[7] "the dye contained in the crayon appears to be benzidine yellow YB which is manufactured by coupling tetraazotized benzidine with acetoacetanilide or a substituted acetoacetanilide. There is a very small amount of color in the crayon. It amounts to about one half of one percent of the total weight of the waxy portion of the crayon".

According to the National Bureau of Standards Brochure CS 130-46, in relation to color material for Art Education in Schools, the subject of pressed crayons, which is the type concerned in this case, "they shall not contain free dyestuff in excess of 0.5 percent. Pressed crayons shall not contain lead, arsenic or other toxic materials in excess of 0.05 percent."

Von Oettingen[8] has shown that benzidine is toxic and can cause methemoglobin in vitro and when ingested in sufficient amount in laboratory animals will cause Heinz bodies to be present in erythrocytes. There has not been any experimental work, known to the authors, of benzidine toxicity when the material is imbedded in wax.

Crayons of the same make were obtained and sent to the National Institute of Health[9] for experimental feeding of cats, which are susceptible animals for the formation of methemoglobinemia. Following oral ingestion

of the test crayons, blood samples were periodically examined, over a 24 hour period, without revealing any methemoglobin. Examination of blood smears revealed no evidence of Heinz bodies.

Therefore there is no positive corroborative evidence in this case to prove that the ingestion of a hard pressed yellow wax crayon was the etiological factor of this child's methemoglobinemia. However the authors feel that further observation along these lines should be made.

The authors are indebted to the Clinical Laboratory of Children's Hospital under the direction of Drs. Lindsay, Rice, Selinger and Cassidy and to Dr. P. A. Neal and Dr. S. Spicer of the National Institute of Health for their able and willing cooperation.

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WETZEL'S GRIDS, A MEANS OF CLINICALLY COMPREHENDING GROWTH AND DEVELOPMENT*

Frank J. Fagan, Jr.

From a broad point of view, the chief aim of parents and that of the pediatrician is to provide the most favorable conditions for the growth and development of children entrusted to their care. From a clinical point of view it is axiomatic that a child who fails to grow and develop properly is not healthy, and that such a child should become the subject of a truly searching medical examination. Wetzel's girds will not furnish an automatic answer as to whether a child is healthy or not, for it may reveal an entirely normal growth and development course in a child with certain major or minor clinical defects. Far outnumbering these children, however, are those in whom growth and development ebb and flow in response to the circumstances of their lives. To my knowledge there is no more simple analysis of these oscillations of growth and development than Wetzel's grids. From the knowledge abstracted from a grid record, the pediatrician may often gain his first suspicion of disease, or he may obtain certain knowledge of oncoming obesity or malnutrition before these states are either subjectively manifest, or evidenced by other tables of height, weight and age relations. Other anthropometrical measurements, such as hip width, chest circumference, leg girth, estimates of thickness of skin and subcutaneous fat, are of no clinical value except in very special cases. The grid may also aid him in evaluating the seriousness of known disease processes and a better judgment of therapeutic response. It will give him the best evaluation of the treatment of obesity and malnutrition.

Wetzel's grids produce a completely individual standard of norm for each individual child. This can be done because it can predict how an individual child will grow and develop if not overly nourished or undernourished, or afflicted with physical or mental disease. *This standard of norm given by Wetzel has very small limits because variations of growth and development inherent in a child's constitution—the individual's inherited physique (true body type), and the individual's own time schedule of normal development—are quantitatively known.*

Wetzel's grids make use of only two anthropometrical measurements:

* Editors Note: Because of recent keen interest shown by members of the staff in Wetzel's Grids, this senior pediatric thesis would seem to have merit. The reader is referred to the recent literature for examples of the Grid or to NEA Service Inc., 1200 W. 3rd St., Cleveland, Ohio for copies. Mr. Fagan is a senior medical student at Georgetown University.

weight and height. These measurements are then placed upon the grid along with the child's age. There is no need of computation in recording, since a scale of pounds and inches is part of the grid, side by side with a scale of metric units. It is not necessary, therefore, that the doctor do more than interpret the curve before him. The measurements can be made and recorded by school teachers, or by mothers of average intelligence. For "big grid" purposes, measurements made at three to six month intervals are adequate, in health.

The big grid is based on the now well substantiated theory (which has only very rare exceptions), that following the pre-school slenderizing process, healthy growth and development proceed so as to keep physique constant, and on a time schedule which, though it may vary from individual to individual, is nevertheless predictable from the record of the past growth of the child. Other charts of height, weight and age simply indicate where a child stands in relation to an average, or in a group of 100, without regard to a child's inherited physique and particular schedule of development. Wetzel's grids tell where the child stands in physique and development in respect to both the average physique and development, and what is more important, where he stands in respect to himself and in what direction his physique and development are headed.

Examination of the grid will reveal that height and weight, whether measured in metric or English units, are recorded as the point of which the weight is the ordinate (distance along the vertical axis), and the height is the abscissa (distance along the horizontal axis). This point establishes the physique channel and the developmental level. To place the child's developmental level in relation to age, a point is placed on the second panel at the same developmental level and at the point where the child's age abscissa intersects it.

Constant physique is indicated on the big grid by channelwise course with variation of less than one-half channel width per ten units of development. Variations of one channel width should not occur within any number of developmental levels.

After the "pre-school" slenderizing process there are two and only two paths of changing physique—the path towards obesity and the path towards malnutrition. An abnormal upward slope (one which varies more than one-half channel width per ten units or more than one channel width in any number of developmental levels) is indicative of one of three possibilities: 1) that the child is leaving his constitutional physique and is headed towards obesity; 2) that the child is recovering from malnutrition; 3) a very unlikely possibility that the child's constitutional physique is undergoing physiologic change. An abnormal slope downward (one that varies more than one-half channel width in ten units, or more than one

channel in any number of developmental levels) indicates that: 1) the child is malnourished, whether or not the food intake is sufficient; 2) the child is recovering from obesity; 3) the very unlikely possibility that the child's constitutional physique is undergoing physiologic change.

A curve of growth and development which shows significant departure from the channel slope indicates simultaneous changes in both nutritional grade and body build. The slope of the curve indicates the nutritional grade, which is optimum at the slope of the grid channels. The projection of any other slope than optimum on the channel axis represents the exact measure of the change in body build.

Aside from the abnormal features of the nutritional grade the various physique channels carry the following implications.

Obese	A_4
Stocky	A_3, A_2
Good	A_1, M, B_1
Fair, but questionable	B_2
Borderline and doubtful	B_3
Frankly poor	B_4

The developmental level, a function of height and weight alone without reference to age, is measured by the grid independently of physique, change in physique or rate of development. The zero base is set about one-half way between the average developmental level at birth and at maturity, and corresponds to the point at which the rate of gain ceases to decrease and begins to increase. For the practicing physician the units are to be considered arbitrary. After the channel course becomes straight, however, these units are directly proportional to the basal heat production. The significance of this is that developmental change and metabolic change go hand in hand in the school years. This should not come as a surprise to those familiar with BMR interpretation in which the normal BMR for the individual is made a function of height and weight also, by use of a power formula for body surface. It is customary also to introduce age in the determination of the normal. Wetzel has demonstrated that age is not a factor in BMR, but only accidentally parallels the increase in metabolic rate, and should not be used in determining normal values of basal heat output. Furthermore, the fact that since 1940 Wetzel's figures for normal BMR have given a more significant norm, one with a more narrow range of variation than that determined from height and weight by power formulae, whether with or without added "corrections" for age, is of considerable clinical significance in hyper and hypothyroidism. The basal heat production may be found related to developmental level in panel III of the grid. Between the time Wetzel stated the relation between

the developmental level and the basal heat output and the verification of the developmental level-calorie relation by studies of the Harvard School of Public Health findings, it was shown that although developmental level was not calculated as a function of surface area by Wetzel, it nevertheless gives a more accurate means of calculating surface area than the power formulae.

In determining diet by means of the big grid, one-third is added to the basal heat output for growth and development and two-thirds for activity and losses. Thus by simply multiplying basal heat output by two, one obtains the caloric requirement of the child necessary to keep his physique and developmental schedule. This resultant figure may be further adjusted upwards or downwards for weight gaining, reducing, or special diets.

Up to this point there have not been discussed any items which are related to age. By consideration of the child's developmental level in relation to his age, his age advancement or retardation may be determined. This may be expressed in terms of the general population, or in terms of his expected schedule. For every developmental level there is a developmental age—the age level on the "auxodrome" panel at which the developmental level crosses the 67% auxodrome. The relation which the developmental age bears to the chronological age, can be best expressed by the fraction: Developmental age/Chronological age. (Example 10/9: Johnny, a nine-year-old boy, advanced one year over the average.) Division, so as to determine this ratio in decimal figures, causes the ratio to lose its clinical value.

The developmental age is of interest in relation to the skeletal age. The estimation of the developmental age from skeletal age is much more time consuming and less understandable. In fact, the whole field of skeletal growth and development will be greatly illuminated by relating the roentgenological findings to the developmental age and to maturity rating, rather than to the chronological age alone. As to the maturity rating, more will be said later.

The developmental age is related to the norm for the general population. More important clinically is the relation of a child's developmental level (or developmental age) to his own expected developmental level. If there is significant lag or advancement, something is amiss. The difference between the actual and expected developmental level is sopken of as specific developmental lag or specific developmental lead, and should not exceed five levels. Furthermore, any child on a more retarded auxodrome than the 82% auxodrome should be provisionally regarded as progressing unsatisfactorily, pending further medical investigation.

Maturity may profitably be considered clinically in two of its aspects: 1) the advent of puberty; 2) the maturity rating. The advent of puberty

may be expected in the neighborhood of the greatest upper curvature of an individual auxodrome, occurring at the time when the growth rate is decreasing most rapidly following the adolescent "spurt". Delayed or premature puberty is often a source of concern. Maturity rating is expressed as the relation of the developmental level to the ultimate developmental level which is predicted from the individual's own auxodrome: Developmental Level at Moment/Ultimate Developmental Level of the child's particular auxodrome. Also of interest is the age at which the child should be virtually 100% mature. Generally speaking, after the period of neutral childhood, which lasts until about the ninth to the tenth and one-half year, girls develop along a more advanced auxodrome, and reach an earlier maturity.

Channel course and auxodrome are independent. There may be any combination of the two. This must be borne constantly in mind.

There are two states that the grid can forecast: oncoming malnutrition and oncoming obesity. Malnutrition, in the broad sense, including intake and utilization defect, will involve a lag in development and a loss of physique. The appearance of these changes on the grid is characteristic. The first manifestation of defective nutrition is a developmental lag, indicated on the grid by a downward swing of the auxodrome. If the defective nutrition persists there will be a slenderizing of physique manifest in one of two ways: if the deficiency is severe, there will be a one-half channel loss within ten developmental levels; if the dificiency is not so severe, but prolonged, there will be loss of channel, but not at the rate of one-half channel per ten developmental levels. Obesity is similarly forecast by departure of physique towards obesity with simultaneous developmental lead.

If the malnutrition or obesity is not complicated by other diseases, the change in channel and auxodrome is not erratic. The grid curves of children with nephritis, marked allergy and severe hyperthyroidism, show marked instability and irregularity.

Children with chronic heart disease do far better than might be expected, unless failure is distinctly evident, in which case, the grid serves as a prognostic guide. Active rheumatic heart disease is usually accompanied by slight but definite changes in channel and auxodrome, even in the absence of failure. Wetzel cites an interesting case of a young boy with no symptoms or signs of rheumatic fever or rheumatic heart disease, who showed only malnutrition not responding to dietary correction and a moderate pharyngitis, and whose EKG showed marked prolongation of the P-R interval. This EKG would not have been taken were it not for the grid.

The grid is of specific value in pediatric diabetic practice. A coöperative

and well controlled child runs a remarkably steady course of development interrupted but slightly by infections and reactions; however, one attack of coma may hold up development for many months. Tolstoy's diabetic regime could hardly be applied to children with a promising degree of success without the use of the grid, and if a child is managed otherwise he would benefit by added attention to growth and development.

Hyperthyroidism poses a most interesting application of the grid. Mildly hyperthyroid children are characteristically B_2 and below, but occasionly B_1's and M's and rarely A_1 channel types are seen. With increased severity they first develop lag in auxodrome, and then there may be loss of physique. As an example of the importance of the metabolic standard, Wetzel cites the case of a suspected hyperthyroid child whose initial BMR when compared to DuBois' standard was plus 8%, but when compared to Wetzel's standard it was plus 17.5%. Some months later the BMR increased to plus 33% (DuBois); plus 44% (Wetzel). Upon treatment with Lugol's the BMR returned to plus 9½% (DuBois); plus 18% (Wetzel). Partially because she showed a favorable grid course at this time, an operation was performed precipitating a thyroid crisis and death. If plus 18% had been considered the true BMR and thiouricil had been available, the surgery would not have been done until the BMR was less than plus 10%.

Cretinism and marked juvenile hypothyroidism are characterized by markedly retarded auxodromes. Mild hypothyroidism should be suspected when there is growth retardation (characteristically without channel shift, or less commonly a reverse shift in relation to malnutrition, i.e., a shift to obesity). A therapeutic trial is justified if these children show a BMR of minus/0% or less repeatedly and with little variation. Here the grid will serve as an excellent prognostic and therapeutic guide, for too much thyroid will cause developmental lag.

Of interest are the grid records of eccentric osteochondrodystrophy, hypogonadism and precocious puberty. Morquio's disease is characterized by channel preservation with an extremely delayed auxodrome; hypogonadism by developmental lag without loss or gain of physique; precocious puberty by developmental lead without loss or gain of physique.

The treatment of obesity with the grid is approached quite simply. Since the developmental level is advanced beyond the individual's auxodrome, the proper developmental level is assumed to be that of the same height in the A_3 or A_4 channel. The diet should be about 10 to 20% over the basal value at this proper developmental level; this figure may be readjusted on the basis of therapeutic response.

The developmental response to proper diet of the malnourished child

is startling if the malnutrition is uncomplicated—exceeding the normal developmental rate by three to six times. The recovery rate of development for one, two, three, channel displacements is three, five, six, developmental levels per month respectively. Failure to respond to adequate diet is indicative of a complicating mental or physical disease. It is surprising the effect that minor physical defects may have. Carious teeth, objectionable tonsils, granular hyperplasia of the pharynx, may or may not affect growth and development. When these defects are corrected, the grid will give the first evidence of therapeutic response and therefore if no response occurs, a much more searching medical and psychiatric study may be instituted months before they might seem indicated without the grid. It is to be stressed that the most common cause of recurrent malnutrition treated at the Fresh Air Camp of Cleveland, was allergy, especially that manifested by the upper or lower respiratory tract. With removal of the allergy or allergen, the return of hearty appetite was startling.

The grid could be of importance in public health work. Some critics maintain that child public health programs are woefully inadequate and are impressed by how small the school health staff is compared with the large number of children in its care. It is their contention that "what is missed" could have been found by more frequent and thorough exams; however, growth failure is the most important and commonly missed entity and this cannot be discovered by methods of physical diagnosis, no matter how often applied. The screening of school children by Wetzel's grid furnishes a better solution to the problem of adequate medical care than merely increasing the school health staff. An outline of screening procedure is given below:

Grid Assessment of Growth, Nutrition and Development

SATISFACTORY	UNSATISFACTORY
About 70%—quick examination indicated.	About 30%—extensive study indicated: Diet Home conditions Laboratory studies Hospitalization Diagnostic therapy

Physical education programs take on a new light when correlated with grid records. By use of the grid, calisthenics and sports may be graded to suit individual physiques, and in like manner exacerbation of disease processes and the mental anxiety of failure, incident to the application of excessive exercise to growth deficient children, may be prevented.

THE BABY GRID

In Wetzel's latest development, the baby grid, the channel system fills the interval of growth and development from the one thousand gram premature, to the channel system of the big grid, along with auxodromes extending up to the third year. This leaves a discontinuity in auxodrome course, from the third to the fifth year.

The fundamental principle of constancy of physique does not apply to the baby grid because of the stoutening process beginning before birth and a slenderizing process which begins fifteen to twenty-one months after conception. Wetzel, however, has determined the nutritional grade for each developmental level, and has thus been able to construct a channel system upon which the optimum course of development is indicated. The preferential paths of development which will extend into the constant physique channels A_1, M and B_1 of the big grid, are indicated by a tri-colored strip: 1) the pink premature strip; 2) the orange full-term strip; 3) the yellow postnatal strip. A baby's course of development should parallel the colored strip just as it should the preferential path of the big grid, except that a little more latitude of change from the preferential path is allowable within short intervals of development. "Ordinarily, shifts of one channel width within twenty levels of forward advancement are allowable, but even these should not persist." (Recall that the corresponding stipulation for the big grid course is one-half channel within ten developmental units.)

The auxodrome course has even more rigid limitations than upon the big grid, being restricted to two or three levels of lag or lead rather than five.

The metabolism panel differs in that, for convenience of diet calculation, the complete calorie allowance is stated in place of the basal heat output. Furthermore, the calories per unit weight are given for the various ranges of developmental level. Of course, these calorie allotments are subject to considerable clinical modification, for even such a common infant activity as crying increases the metabolic rate one hundred per cent.

In addition to modification of the features of the big grid, there are also added accessories: 1) a subsidiary panel of chest circumference plotted against length; 2) head circumference plotted against age; 3) a "Useful Data" table upon which nutrition, blood volume and surface area are related to developmental level, along with vitamin and mineral allowances, not so related. The most valuable part of the Useful Data table, perhaps, is the formula allowance of carbohydrate, fat and protein for premature infants. This is based upon the proportionment of calories as 51–29–20% carbohydrate, fat, and protein, respectively.

During the first six months any arrest in weight which persists for a week has pathological significance. Measurements of height, however, have a more limited value, as the measurement of an infant's height is subject to more error. Therefore, for grid purposes a practical schedule for the measurement of height and weight is every second week for the first year, every third for the second year, and every fourth week for the third year, a total of fifty-six measurements.

Wetzel's latest article gives baby grid curves resultant of feeding difficulty, overeating, measles, congenital adrenal cortical deficiency associated with androgen hypersecretion, prematurity, and even domestic upset.

Wetzel tenders a fitting note of conservatism in anticipation of excessive claims for his grid, "No diagnosis is sought from or rendered by the grid. . . . Specific pathologic events are entirely outside its field. . . . Consequently it must be finally emphasized that interpretation of grid curves lies solely within the province of the physician, who can take results of his own examination and grid rating into joint account."

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SICKLE CELL ANEMIA

Case Report No. 92

John Paul Jones, M.D. R. W. 47-523

R. W. was admitted to the hospital on the morning of January 14, 1947 with the chief complaint of generalized abdominal pain which began suddenly the day before and which persisted intermittently. There was no nausea, vomiting or diarrhea and the child offered no other complaints. Except for chicken pox, measles and whooping cough the past history was negative. There was no history of frequent respiratory infections. Feeding and developmental history were negative. The family history was negative except for the fact that a sibling, aged 4 years, has sickle cell anemia.

Physical examination on admission revealed a well-developed, colored male, aged 6 years, who appeared acutely ill and who complained of generalized abdominal pain. The temperature was 101.4 degrees F. (R), pulse 130 per minute and the respirations 36 per minute. The respirations were grunting in character with dilatation of the alae nasi. The nail beds, conjunctiva and oral mucous membranes were pale. The tonsils were enlarged and moderately injected. The anterior cervical lymph nodes were palpable. The lung fields were clear. The heart was definitely enlarged to the left, the apex being in the fifth intercostal space, well beyond the mid-clavicular line. There was a loud, somewhat rough, systolic murmur which was heard over the entire precordium but which was maximal in the second left interspace. The abdomen was full and there was tenderness to deep palpation and slight generalized rigidity. There was tenderness in the right costo-vertebral angle. Peristalsis was active. The liver edge was firm and palpable 6 cm. below the costal margin.

A hemogram done on admission revealed the red blood count to be 2.9 million, hemoglobin 7.5 grams and white blood count of 26,000 with 78 per cent polymorphonuclear cells. The venous pressure determination was 115 mm. normal saline. Examination of the chest by X-ray revealed the heart to be enlarged to the left and a bulge in the region of the pulmonary conus. Repeated urinalyses were negative. An electrocardiographic tracing showed evidence of left ventricular hypertrophy. The P-R interval was within normal limits. The corrected sedimentation rate on the day of admission was zero. This was repeated three days later and was 5 mm. per hour. Kahn and Mazzini tests were negative. The icterus index was 6 units. No sickling of the erythrocytes was seen on the fresh smear at the time of admission, but after 24 hours 65 per cent of the cells showed this phenomenon.

Two hours after admission the patient was given a transfusion of 220 cc. of citrated whole blood. Ten hours later he was given a second transfusion of 150 cc. of whole blood. On the day following admission, the abdomen was soft and non-tender. The temperature was normal 48 hours after admission and remained normal until the patient was discharged. On the seventh hospital day he was given a third transfusion of 200 cc. of whole blood and was discharged soon thereafter to the Hematology clinic. At the time of discharge the hemoglobin was 11.5 grams. The roentgenogram revealed the heart to be considerably smaller than on admission, although it was still somewhat enlarged to the left. Liver dullness had approached normal. The cardiac murmur persisted.

DISCUSSION

In 1910 Herrick[1] first described the characteristic hematological and clinical features of sickle cell anemia. He described dyspnea, palpatation, and polyarthritis in a patient with an enlarged heart, a loud systolic murmur over the precordium and an accentuated pulmonic second sound. In 1911 Washburn[2] described a third case, considered this type of anemia a disease entity and postulated that it was probably inherited. The sickling phenomenon was discovered by Emmel[4] in 1917 and he demonstrated this phenomenon in the patient's father. Mason[5] in 1922 believed that the disease was peculiar to the negro race and first used the term "sickle cell anemia." During the next year Huck[6] described in detail the hematological findings and noted edema of the ankles, enlargement of the liver, low blood pressure and a protodiastolic gallop in his two patients. In 1923 Sydenstricker[7] first described enlargement of the heart confirmed by X-ray. King and Janeway[8] were first to note an abnormality in the electrocardiogram and described a case with prolongation of the P-R interval. Post mortem findings have been reported by many writers and the principal cardiac findings have been hypertrophy and dilatation. Cooley and Lee[9] proposed the term "sicklemia" for the sickling phenomenon which occurs in individuals who show no clinical features of the disease. This trait has been observed in six to ten per cent of negroes[10, 11]. In 1939 Bunting[12] reported the sedimentation rate of the erythrocytes as being slow. Sickle cell anemia rarely occurs in white persons[13]. In 1942 Klinfelter[14] reviewed the literature and described twelve patients with sickle cell anemia. He noted systolic murmurs at the apex in all twelve patients, diastolic murmurs over this area in nine patients, and described a systolic murmur at the base over the pulmonic area. Fifty per cent of his patients had a prolonged P-R interval. The cardio-thoracic ratio was increased in every case. In 1945 Winsor and Burch[15] studied 25 patients with active sickle cell anemia and reported the

pathologic changes found at nine autopsies. They noted cardiac enlargements in 95 per cent of the cases and described systolic and diastolic murmurs at the aortic, pulmonic and mitral areas. The most frequent microscopic pathologic changes were pronounced interstitial edema and degeneration of the sarcoplasm in the cardiac muscle.

Pallor of the nail beds, conjunctiva and the oral mucous membranes, abdominal tenderness, enlargement of the heart and liver, a loud rough systolic murmur and elevated pulse rate, temperature and respiratory rate are common findings in sickle cell anemia and indicated the diagnosis in this case. The race of the patient and the history of the abnormality in a sibling helped to corroborate the diagnosis. Abdominal tenderness and rigidity, an elevated white blood-count with leucocytosis and fever might suggest a surgical condition in the abdomen but this possibility was thought to be ruled out on the basis of the absence of nausea and vomiting, a negative rectal examination, the slight degree of rigidity and the fact that the patient did not appear toxic. Acute rheumatic fever with mild congestive heart failure was considered at the time of admission due to the fact that the sickling phenomenon could not be demonstrated on the fresh smear. The enlarged liver, and the cardiac signs closely resembled those of rheumatic heart disease.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by E. Clarence Rice, M.D.

Case Report No. 93

Fernando Leyva, M.D. J. T. G.
Lois Murphy, M.D.

A five-week old white male was admitted to The Children's Hospital because of vomiting and hematuria of twenty-four hours' duration. The emesis followed feeding. The hematuria was noticed on several occasions during the 24 hours before admission. Bruises had been present for a few days and there was no known trauma. The child's skin had had a yellowish green discoloration of varying intensity since birth. There were usually five to six gray to green colored and constipated stools passed daily.

The mother and father were living and well. There were no siblings. The maternal grandmother had diabetes but the family history was otherwise non-contributory.

The patient had a normal delivery at term at the Georgetown University Hospital with a birth weight of 7 lbs. 14 oz. He was breast fed and seemed to have a good appetite.

Physical examination revealed a fairly well-nourished and developed white male infant who did not seem to be in any acute distress. The skin was markedly jaundiced with a peculiar mottling over the chest. An erythematous rash was noted between the folds of the neck. Bruises were found on the right elbow, right knee and dorsum of the left hand. The lymph nodes appeared normal. The head seemed normally shaped; the fontanelle was 3.5 cm. in diameter and was full. The sclerae showed jaundice. The ears, nose and throat appeared normal. No abnormal pulmonary signs were noted. The heart rate was very slow during rest but speeded up with activity. The position of the left border indicated slight enlargement. The tones were of good quality and no murmurs were heard.

The abdomen was enlarged and the liver could be palpated 8 cm. below the infracostal border. A mass on the left upper quadrant extended from the left infracostal margin to the anterior superior iliac spine; it was solid and round and more suggestive of kidney than spleen. The weight on admission was seven pounds six ounces and the temperature 97° C.

Examination of the blood revealed 3,100,000 erythrocytes, 27,200 leukocytes with 65% neutrophiles, 31% lymphocytes and 4% monocytes. Thrombocytes were estimated at 300,000. The red cells showed slight microcytosis and achromia. Bleeding time was less than one minute, coagulation time four minutes and prothrombin time 29% of normal. Blood serological test showed a positive standard Kahn, with an icterus

index of 73; the Van den Bergh was immediate and direct with 8.25 mgm. percent bilirubin.

Six hours after admission the child developed respiratory distress and a marked bradycardia. In spite of various stimulants and the administration of oxygen, he expired seven hours after admission.

DISCUSSION

Dr. W. S. Anderson: This case brings to discussion the differential diagnosis of jaundice in the newborn infant. There are several points in the history on which I would like to comment. First of all, there is the "so-called" hematuria. Since there was no examination of the urine, this may have been due to bile in the urine, and reported as blood. On the other hand in view of the hypoprothrombinemia and clinical evidence of bruising, it may have been a manifestation of generalized bleeding, with the full fontanelle possibly due to an intracranial hemorrhage.

The baby was reported as well developed and nourished and yet in spite of a birth weight of 7 lbs. 14 oz. the baby weighed only 7 lbs. 6 oz. at 5 weeks. The fontanelle was full, and this should be taken seriously because the baby had been vomiting, and was not too well hydrated. This probably manifested intracranial bleeding, but meningitis has to be kept in mind. The mass in the right quadrant was obviously liver, and on the left side, it may have been spleen; I do not believe it was a kidney mass. However the spleen in jaundice of the newborn is rarely that large, and no splenic notch was described. In this infant the temperature was subnormal, and we know that fever is a very unreliable sign during the neonatal period. Some of the more seriously ill infants in this age group may have subnormal temperatures, even with overwhelming infections. The elevated white count may represent superimposed infection or possibly dehydration. The anemia would fit in with any of these. The low prothrombin time would fit in with any type of jaundice, and cause the bleeding manifestations. The Van den Bergh would be in keeping with an obstructive type of jaundice.

The positive Kahn in this age group may or may not fit into the clinical picture. It could explain the jaundice on the basis of a syphilitic hepatitis. However, we know that a serology is sometimes unreliable in this age group, and no time was available to study this from a quantitative angle, which would show an increasing titer in truly positive cases.

In this case, I believe that we are dealing with an obstructive type of jaundice. I am not sure whether or not the obstruction is complete or not, for the stools varied from gray to green in color, and no chemical determinations were made. Congenital malformation of the biliary tract could explain the whole picture although the jaundice is apt to appear later than the first month of life. The positive Kahn could be purely incidental and

the congenital malformation of the biliary tract the primary difficulty. As a second diagnosis we should consider congenital syphilis with syphilitic hepatitis. Other less likely diagnoses would include overwhelming sepsis, some form of unclassified hemolytic anemia of the newborn, and lastly a low grade form of erythroblastic anemia which had passed the acute phase.

In summary my primary diagnosis would be congenital malformation of the biliary tract with the positive Kahn incidental; and in the following order, congenital syphilis with hepatitis, and lastly sepsis.

POST MORTEM EXAMINATION

Dr. F. H. Leyva: The anatomical findings in this case were:

1) Developmental anomalies of the biliary system:
   a) Absence of the gallbladder.
   b) Absence of the extrahepatic system.
   c) Extensive biliary cirrhosis.
2) Intracranial and pulmonary hemorrhage.
3) Post mortem absence of blood clots.
4) Marked jaundice.

The term "absence of the biliary ducts" is somewhat inadequate; it would be preferable to use atresia or non-demonstrable bile ducts. In some cases the extrabiliary ducts and the gallbladder are completely obliterated and represented by a fine cord of fibrous tissue, occasionally being very hard to identify. This type of malformation is believed to represent an arrest in development, consisting in a failure of the fetal bile ducts to become canalized. This obliteration may be partial or complete and may involve the common duct, the hepatic, the cystic or all of them, therefore the different anatomical types noted. It seems very important to recognize these types of malformations, since many cases are susceptible to a surgical correction. Naturally our case is one of the inoperable type a biliary atresia associated with rather advanced biliary cirrhosis.

Dr. Rice: Jaundice of the newborn which persists after the first few weeks of life and cannot be accounted for by infection or inspissated bile occluding the biliary passages should on the basis of the history, physical and laboratory examinations suggest the possibility of intra-or extrahepatic obstruction. Anomalies such as have been described today are fortunately uncommon and the chances of finding an extrahepatic obstruction for which surgery can bring relief are sufficiently good as to warrant the pediatrician and surgeon to assume the risk of surgical intervention. The increasing number of children who are alive today following operation for the relief of biliary obstruction during the first year of life is evidence of the wisdom of this procedure. In those patients for whom relief has been impossible to obtain, death is often due to hemorrhage because of a coagulation defect secondary to the marked liver damage.